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10/599,351	08/22/2008	Frank Larsen	LARSEN-2	7261

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EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/599,351	LARSEN, FRANK	
	Examiner	Art Unit	
	SAMUEL C. WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-17* is/are allowed.

6)☒ Claim(s) *18-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Preliminary Remark

In the Written Opinion of the International Searching Authority for international application PCT/IB2005/000763, which corresponds to the instant application, the following statement appears:

> 3.4 However the subject matter of claim 1 cannot be regarded as involving an inventive step because the claim extends to methods that do not solve the technical problem and are therefore not inventive:
>
> 3.4.1 If the sequencing reaction of step (b) is performed with the non-labelled primer non-labelled sequencing products will be generated that are derived from the target and the non-target sequence since the primer binds to and can be extended along the target sequence as well as the non-target sequence. If subsequently in step (d) the sequence of the non-first labelled sequencing products is determined it represents a mixture of target and non-target sequences.

The Examiner disagrees with this assessment, since claim 1 requires that the "first labeled nucleotide" is only incorporated into the primer hybridized to the target or the non-target, but not both. Therefore, the sequencing reaction will produce some sequencing products bearing the "first labeled nucleotide" and some sequencing products that do not. One would be able to distinguish the two sets of sequencing products on that basis.

The Written Opinion further states:

3.4.2 If in the method fluorescent labels are used and the sequencing is performed with pyrosequencing (see description and claim 22) the person skilled in the art is confronted with the problem that in the sequencing method, which is performed without the use of a label and in which the release of pyrophosphate is detected during the synthesis of the sequencing product (D3 p. 1250 left col.), he has to find a way to detect the fluorescent label attached to the primer as well. Additionally he has to find a way to differenciate between the pyrophosphate that is released during the sequencing reaction of the target sequence and the pyrophosphate that is released during the sequencing reaction of the non-target sequence that takes place with the unlabelled primer.

3.4.3 If the first label is biotin and the biotin is bound to a solid phase (claim 4), given the fact that the biotin is bound to the nucleotide that forms the 3' end of the primer, said primer cannot be extended in a sequencing reaction using a polymerase.

It is noted however that claim 22 does not state that the labels are fluorescent. The specification describes that the label may be a member of a "ligand-affinant" pair allowing for the physical separation of the target and non-target sequence. In fact, the specification at page 18 indicates this is essential in pyrosequencing embodiments of the invention. With regard to item 3.4.3, it is respectfully submitted that while the solid phase, which is not recited in the claim, might sterically hinder the polymerase, there is no reason why the template/primer complex need remain bound to the solid phase during the sequencing reaction if such were the case. For example, use of a cleavable linker between the biotin and the nucleotide, or addition of excess biotin to drive the primer/template complex off the solid phase, could be used to remove the nucleic acid from the solid phase prior to the sequencing reaction.

Therefore, while the Examiner does have some complaints with regard to claim 22 (see below), he disagrees with the general sentiment of the Written Opinion that the claimed methods are inoperable.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. As claim 18 is the more complicated situation, this claim will be discussed last.

Claim 20 recites the limitation "the second nucleic acid" in line 5. There is insufficient antecedent basis for this limitation in the claim. Claim 20 depends from claim 1, which refers to a "target nucleic acid" and a "non-target nucleic acid". Likewise, claim 19, which depends from claim 20, refers to a "target nucleic acid" and a "non-target nucleic acid". Because claims 19 and 21 depend from claim 20, they are rejected for the same reason. Applicant is advised to amend claim 20 to change "the second nucleic acid" to "the non-target nucleic acid".

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a separation of the first-labeled primer/nucleic acid complex from the non-first-labeled primer/nucleic acid complex. This would clearly be essential because pyrophosphate sequencing is based on detection of the pyrophosphate released as nucleotides are incorporated into a polynucleotide by a polymerase, and there would be no way to differentiate between the

pyrophosphate released by the "target" sequencing reaction from the pyrophosphate released by the "non-target" sequencing reaction, unless the primer/target template and primer/non-target template were separated prior to the sequencing step. In fact, the specification itself indicates this is essential at page 18, 2nd and 4th paragraphs:

> Alternatively the separating step may be performed after step (b) and before step (c), in order to separate the first-labelled primer/nucleic acid sequence complex from the non-first-labelled primer/nucleic acid sequence complex before performing the sequencing reaction.

> In embodiments where the method of sequencing comprises a real-time method such as pyrosequencing, the sequencing reaction and sequence determination steps (steps (c) and (d)) are substantially simultaneous. In these embodiments, the separating step must be performed after step (b) and before step (c).

In addition, claim 22 is generally confusing as one would have to "select" a labeled nucleotide in the beginning (assuming "select" means "choose" as opposed to "capture"). In any event, one does not "label" the sequencing products of a pyrophosphate sequencing reaction, since product of such a reaction is pyrophosphate, not a ladder of sequencing products as is the case for Sanger or Maxam-Gilbert type sequencing.

The examiner would suggest the following language for claim 22:

A method for determining a haplotype of a subject comprising the steps of:

providing a sample comprising DNA from the subject comprising a target locus on a first chromosome of a chromosome pair and a non-target locus on the second chromosome of the chromosome pair, wherein the target locus and non-target locus

each comprise two or more single nucleotide polymorphisms and wherein the subject is heterozygous at each single nucleotide polymorphism;

providing a primer that hybridizes to the target locus and the non-target locus upstream of the first single nucleotide polymorphism;

providing a first labeled nucleotide that is complementary to the nucleotide of the first single nucleotide polymorphism in either the target locus or the non-target locus, wherein the label is a member of a ligand-affinant pair;

contacting the sample, the primer and the first labeled nucleotide under conditions to hybridize the primer to the target locus and the non-target locus and to incorporate the first labeled nucleotide into the primer hybridized to either the target locus or the non-target locus, but not both;

separating the target locus/primer complex from the non-target locus/primer complex using the incorporated first labeled nucleotide;

extending the primer of the target locus/primer complex and/or the non-target locus primer complex in a pyrophosphate sequencing reaction to thereby determine a haplotype of the subject.

As to claim 18, since the method is now dealing with a "plurality" of non-target sequences, it is not understood how one would discriminate among the sequencing products derived from the various non-target sequences, since none of these would comprise a distinguishing label. In the case of claim 1, there were only two populations: sequencing products derived from the target sequence and sequencing products

derived from the non-target sequence, and only one of these populations would comprise the "first labeled nucleotide". Hence, these populations could be distinguished. In claim 18, it is clearly recited that the target sequences that give rise to labeled sequencing products (step b: "wherein each first labeled nucleotide is complementary to a first template nucleotide comprised in the first region of dissimilar sequence of a target nucleic acid under conditions to incorporate the first labelled nucleotide into the primer hybridised to the target nucleic acid sequence").

Thus, as the non-target sequences do not result in distinguishably labeled sequencing products, it is not clear how one would distinguish among the products derived from the plurality of non-target sequences (see step d: determining at least a portion of the sequence of each different first-labelled sequencing product and/**or** each non-first-labelled sequencing product).

Applicant is advised to strike "and/or each non-first-labelled sequencing product". Also, the last word of the claim should be "sequences", not "sequence".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Daprich et al (US 2001/0031467).

With regard to claims 23 and 25, Dapprich taught methods for separating maternal and paternal alleles comprising multiple heterozygous polymorphisms. In one embodiment, Dapprich taught providing an oligonucleotide hybridizing to each allele upstream of two single-nucleotide polymorphisms, as well as a labeled nucleotide (e.g. biotinylated "A"; see paragraph [0049] and figure 3) complementary to the first polymorphism of one allele, along with other nucleotides (e.g. figure 3: G, C and T are also provided) and a DNA polymerase (implicitly taught by "enzyme" in figure 3 and "enzymatically elongated in a 5'-3' direction" in paragraph [0048];) to incorporate the labeled nucleotide (see figures 1-3 and paragraphs [0044]-[0049]).

It is noted that claim 25 is construed as requiring only one or more of the additionally recited elements based on the "and/or" language.

With regard to claim 24, Dapprich also taught (as an alternative to a biotinylated nucleotide) a fluorescein-modified nucleotide to effect separation (paragraph [0103]).

With regard to claims 23-25, Dapprich taught providing the invention as a kit (paragraph [0023]).

Conclusion

Claims 1-17 are allowed.

The closest prior art would be either Stanton (WO 01/90419) or Dapprich et al (US 2001/0031467). The teachings of Dapprich have been discussed. Stanton also taught separating one allele from another allele by hybridizing an oligonucleotide to both and extending in the presence of a biotinylated nucleotide complementary to one allele, thus allowing separation (page 65). Stanton also taught that following separation, the

captured allele (or the non-captured allele) could be genotyped to determine the haplotype.

Neither Stanton nor Dapprich taught the same primer used to incorporate a capture moiety was further used as a sequencing primer, nor is such suggested by the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Primary Examiner
Art Unit 1637